

**Amendments to the Claim:**

This listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of Claims:**

1. (Currently Amended) A method of stimulating the immune system of a subject which comprises administering to the subject an immunologically effective amount of an isolated immunostimulatory molecule which comprises at least one oligonucleotide strand which comprises

(1) at least one nucleotide sequence comprising a plurality of nucleotides, each nucleotide comprising a nucleobase, and thereby also comprising at least one CxG dinucleotide unit or analogue thereof,

in which there are no more than seven nucleobases in each oligonucleotide strand,

wherein in said analogue, (1) cytosine is replaced with a cytosine analogue which is a pyrimidine other than thymine or uracil, and/or (2) guanine is replaced with a guanine analogue which is a purine other than adenine, and

(2) at least one covalently incorporated lipophilic group.

2. (Original) The method of claim 1 in which element (1) comprises a CxG dinucleotide unit.

3. (Previously Presented) The method of claim 1 in which the CxG dinucleotide unit is a CpG dinucleotide unit.

4. (Previously Presented) The method of claim 1 in which at least one lipophilic group is a strongly lipophilic group.

5. (Previously Presented) The method of claim 1 in which at least one lipophilic group is a highly lipophilic (Meylan) group.

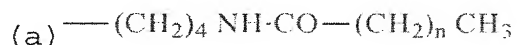
6. (Previously Presented) The method of claim 1 in which at least one lipophilic group has a predicted logP, according to the Meylan algorithm, of at least 4.

7. (Previously Presented) The method of claim 1 in which at least one lipophilic group has a predicted logP, according to the

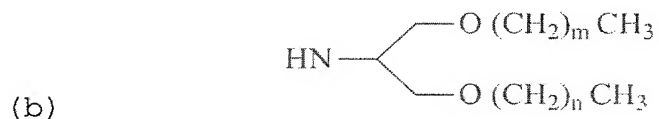
Meylan algorithm, of at least 7.

8. (Previously Presented) The method of claim 1 in which at least one lipophilic group has a predicted logP, according to the Meylan algorithm, of at least 10.

9. (Previously Presented) The method of claim 1 in which at least one lipophilic group is selected from the group consisting of



where  $n$  = an integer with values ranging from 6 to 26,



where  $m$  and  $n$  are independent integers with values ranging from 6 to 26,

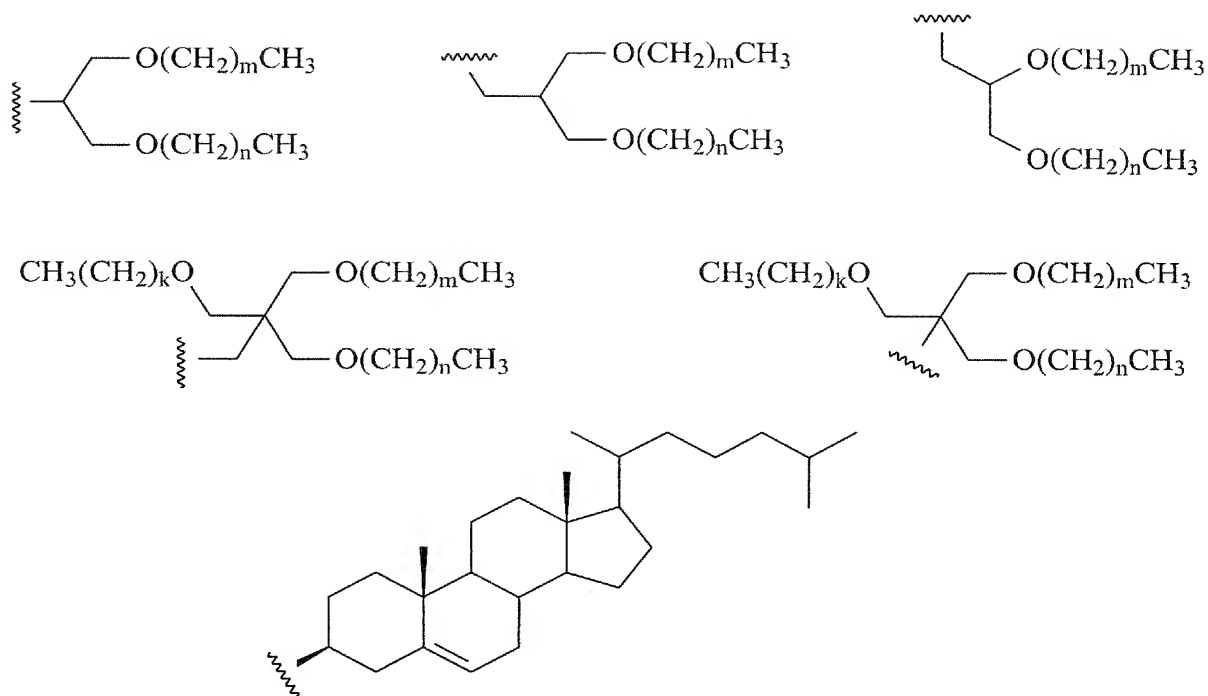
(c)

-XR wherein X is -O-, -S-, or -NH- and -R is aliphatic, and

(d)

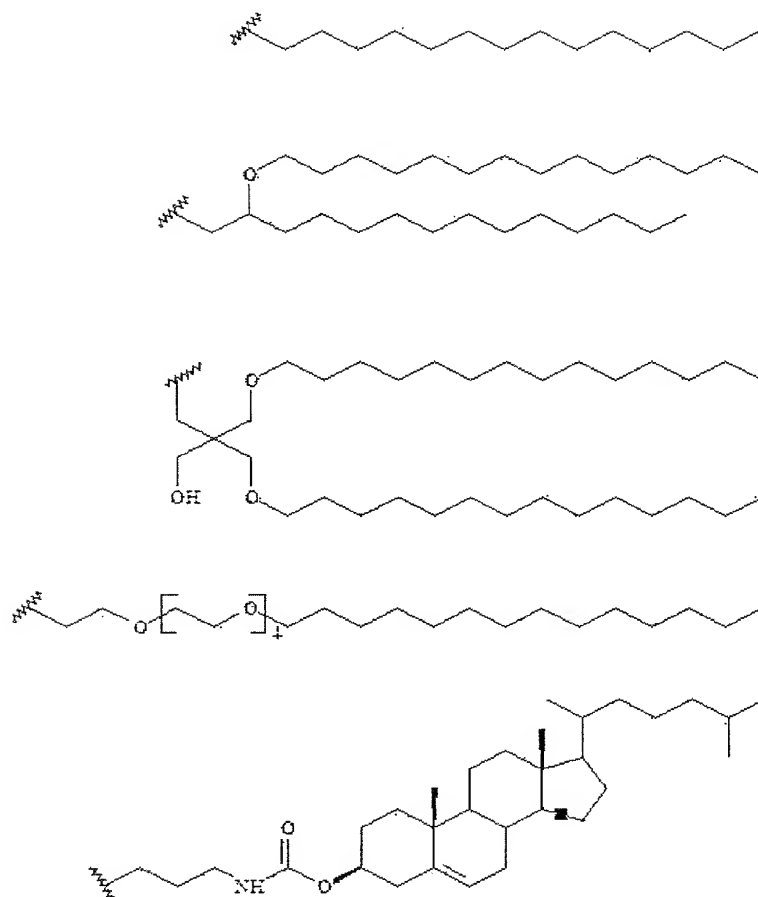
-XR wherein X is -O-, -S-, or -NH- and -R is at least partially aromatic.

10. (Withdrawn) The method of claim 9 where -R is a group selected from the group consisting of one of the following structures:



where  $m$ ,  $n$ , and  $k$  are independent integers with values ranging from 3 to 30.

11. (Currently Amended) The method of claim 1 in which at least one lipophilic group is one of the lipophilic groups depicted in ~~Fig. 2~~ below



12. (Previously Presented) The method of claim 1 where said molecule comprises at least two lipophilic groups.

13. (Original) The method of claim 12 where said molecule comprises at least two strongly lipophilic groups.

14. (Original) The method of claim 12 where said molecule comprises at least two highly lipophilic (Meylan) groups.

15. (Previously Presented) The method of claim 1 in which

there are fewer than 8 nucleobases on each nucleotide strand.

16. (Original) The method of claim 15 in which there are fewer than 5 nucleobases on each nucleotide strand.

17. (Previously Presented) The method of claim 1 in which each of the nucleobases is selected from the group consisting of adenine, guanine, thymine, cytosine, uracil, and hypoxanthine.

18. (Previously Presented) The method of claim 1 in which each of the nucleobases is selected from the group consisting of adenine, guanine, thymine, and cytosine.

19. (Previously Presented) The method of claim 1 wherein at least one nucleotide comprises a nucleobase-carbohydrate nucleoside.

20. (Original) The method of claim 19 in which the carbohydrate is a monosaccharide.

21. (Original) The method of claim 19 in which the number of carbon atoms in the monosaccharide is 3-8.

22. (Original) The method of claim 21 in which the monosaccharide is a pentose.

23. (Previously Presented) The method of claim 20 in which the monosaccharide is an aldose.

24. (Previously Presented) The method of claim 20 in which the monosaccharide is cyclized.

25. (Original) The method of claim 19 in which the monosaccharide is a pyranose.

26. (Original) The method of claim 20 in which the monosaccharide is a ribose or a 2-deoxyribose.

27. (Previously Presented) The method of claim 1 in which all of the nucleotides of one strand comprise a nucleobase-carbohydrate nucleoside.

28. (Previously Presented) The method of claim 1 in which at least one nucleotide further comprises a phosphate.

29. (Original) The method of claim 28 in which at least one nucleotide comprises one and only one phosphate.

30. (Original) The method of claim 29 in which at least one strand is DNA or RNA.

31. (Previously Presented) The method of claim 1 in which at least one lipophilic group is covalently incorporated into a free end of at least one strand.

32. (Previously Presented) The method of claim 1 in which at least one lipophilic group is covalently incorporated into the 3' end of at least one strand.

33. (Previously Presented) The method of claim 31 in which the lipophilic group is attached to the end through a phosphate group.

34. (Withdrawn) The method of claim 1 in which at least one lipophilic group is incorporated into an internucleoside linkage.

35. (Previously Presented) The method of claim 1 in which at least one lipophilic group is a substituent of a nucleobase.

36. (Withdrawn) The method of claim 1 in which at least part of the oligonucleotide has a backbone which differs from that of DNA and RNA.

37. (Withdrawn) The method of claim 36 in which the backbone differs in that the internucleoside linkage is not a phosphate group.

38. (Withdrawn) The method of claim 36 in which the backbone differs in that at least one nucleotide is a non-normal nucleotide which does not comprise ribose or 2-deoxyribose.

39. (Withdrawn) The method of claim 38 in which the non-normal nucleoside comprises a sugar.

40. (Withdrawn) The method of claim 38 in which the non-normal nucleotide does not comprise a sugar.

41. (Withdrawn) The method of claim 40 in which the oligonucleotide is at least partially a PNA oligomer.

42. (Withdrawn) The method of claim 40 in which at least one non-normal nucleotide comprises a non-normal nucleoside of the form

nucleobase-O-alkyl

where the -O-alkyl is the residue of a polyol, and the alkyl is

not more than 6 carbon atoms.

43. (Withdrawn) The method of claim 42 wherein the polyol is glycerol, and hence the alkyl is 3 carbon atoms.

44. (Withdrawn) The method of claim 36 in which at least non-normal nucleoside is bound to a phosphate group.

45. (Withdrawn) The method of claim 44 in which there are two adjacent such non-normal nucleosides and the internucleoside linkage between them is a phosphate group.

46. (Withdrawn) The method of claim 44 in which there are two adjacent such non-normal nucleosides and the internucleoside linkage between them is

-phosphate group-linker Z-phosphate group-,

where linker Z is aliphatic.

47. (Withdrawn) The method of claim 46 in which linker Z is of the form  $-\text{[small alkyl-O]}_n$ , where n is 1 to 20, and small alkyl is not more than 6 carbon.

48. (Withdrawn) The method of claim 47 in which linker Z is  $-\text{[CH}_2\text{CH}_2\text{O]}_n-$ .

49. (Withdrawn) The method of claim 1 in which the dinucleotide unit comprises a non-natural nucleoside, or an internucleoside linkage which is not a phosphate group.

50. (Withdrawn) The method of claim 1 in which the CxG dinucleotide unit comprises two non-natural nucleosides and the internucleoside linkage between them is a phosphate group.

51. (Withdrawn) The method of claim 49 in which the dinucleotide unit comprises two non-natural nucleosides and the internucleoside linkage between them is

-phosphate group-linker Z-phosphate group-,

where linker Z is aliphatic.

52. (Withdrawn) The method of claim 51 in which linker Z

is  $-\text{[CH}_2\text{CH}_2\text{O]}_n-$  and  $n$  is 1 to 20.

53. (Withdrawn) The method of claim 49 in which the dinucleotide unit is a PNA oligomer.

54. (Withdrawn) The method of claim 49 in which the dinucleotide unit is a GNA oligomer.

55. (Previously Presented) The method of claim 1 in which the molecule lacks double stranded structure.

56. (Previously Presented) The method of claim 1 in which the molecule has at least some double stranded structure.

57. (Cancelled)

58. (Previously Presented) The method of claim 1 in which there are no more than four nucleobases in each oligonucleotide strand.

59. (Previously Presented) The method of claim 1 in which the molecule further comprises at least one epitope.

60. (Original) The method of claim 59 wherein at least one epitope is a carbohydrate epitope.

61. (Previously Presented) The method of claim 59 wherein at least one epitope is a peptide epitope.

62. (Previously Presented) The method of claim 59 wherein at least one epitope is a B-cell epitope.

63. (Previously Presented) The method of claim 59 wherein at least one epitope is a T-cell epitope.

64. (Previously Presented) The method of claim 59 wherein at least one epitope is a MUC1 epitope.

65. (Previously Presented) The method of claim 1 in which the oligonucleotide is cyclized, so as to lack a free end, and the lipophilic groups are incorporated elsewhere in the molecule.

66. (Previously Presented) The method of claim 1 where said molecule which comprises two or more segments, each segment consisting of nucleosides joined to each other by short internucleoside linkages, each segment being joined to at least one other segment by a long internucleoside linkage,

at least two of said segments each comprising at least one CxG



dinucleotide unit or analogue thereof.

67. (Original) The method of claim 66 in which said segments are connected by said internucleoside linkages to form one or more linear chains.

68. (Original) The method of claim 66 in which two or more segments are cyclized by two or more internucleoside linkages.

69-71. (Cancelled)

72. (Previously Presented) The method of claim 1 where said nucleotide sequence comprises at least one pair of adjacent thymine nucleobases which are dimerized to form a thymine dimer.

73. (Previously Presented) The method of claim 1 in which at least one lipophilic group is covalently incorporated into the 5' end of an oligonucleotide strand.

74. (Previously Presented) The method of claim 1 in which the molecule does not have cytotoxic activity against cancer cells.

75. (Previously Presented) The method of claim 1 in which the subject is not suffering from a cancer.

76. (Previously Presented) The method of claim 1 in which the subject is not being medicated with any other cancer preventative.

77. (Previously Presented) The method of claim 1 in which the molecule potentiates the specific innate immune response to a pathogen or cancer already present in the subject.

78. (Previously Presented) The method of claim 1 which further comprises administering a pharmaceutical composition comprising an immunogen to the subject, said molecule potentiating the specific elicited immune response to said immunogen.

79. (Original) The method of claim 78 in which the molecule and the immunogen are administered simultaneously.

80. (Original) The method of claim 79 in which the molecule and the immunogen are administered in the same composition.

81. (Original) The method of claim 78 in which the immunostimulatory oligonucleotide molecule is also an immunogen

which elicits a specific immune response protective against said pathogen or cancer.

82-99. (Cancelled)

100. (Previously Presented) The method of claim 1 where none of the internucleoside linkages is selected from the group consisting of poly(N-vinyl), poly (methacryloxyethyl), poly(methacrylamide), and poly(etheylenimine).

101. (New) The method of claim 1 wherein the nucleotide sequence consists of two nucleotides.

102. (New) The method of claim 1 wherein the nucleotide sequence consists of three nucleotides.

103. (New) The method of claim 1 wherein the nucleotide sequence consists of four nucleotides.

104. (New) The method of claim 1 wherein the nucleotide sequence consists of five nucleotides.

105. (New) The method of claim 1 wherein the nucleotide sequence consists of six nucleotides.

106. (New) The method of claim 1 wherein the nucleotide sequence consists of seven nucleotides.

107. (New) A method of stimulating the immune system of a subject which comprises administering to the subject an immunologically effective amount of an immunostimulatory molecule which comprises at least one oligonucleotide strand which comprises

(1) at least one nucleotide sequence comprising a plurality of nucleotides, each nucleotide comprising a nucleobase, and thereby also comprising at least one CxG dinucleotide unit or analogue thereof,

in which there are no more than seven nucleobases in each oligonucleotide strand,

wherein in said analogue, (1) cytosine is replaced with a cytosine analogue which is a pyrimidine other than thymine or uracil, and/or (2) guanine is replaced with a guanine analogue which is a purine other than adenine, and

(2) at least one covalently incorporated lipophilic group.